REMARKS

Election/Restriction – 35 USC 121 & 372

Applicants elect Group I – unknown - drawn to claims 1-33.

Traverse

Until the claims are restricted further, as these are all claims present in the application, there appears no reason to traverse this restriction as the groups are not yet determined such that traverse seems appropriate.

Inventorship

Also as no claims are cancelled or withdrawn, Applicants will refrain on inventorship modification until the claims are better determined so that also can be done, if needed.

Rejoined

Rejoinder of the claims of all claims is requested, when appropriate, as the scope of these claims is coextensive with Formula (I). Applicants will amend these claims to maintain this relationship when and if the elected claims are further amended.

Species Election

To be fully responsive, Applicants elect as a species, the composition of Example 13 (pgs 87-88) that is a PEHAM dendrimer with piperazine, G2, C = PETGE; IF = OH; EX 1-3 = piperazine; BR 1-2 = PETGE; and TF = Amine. This species is present in claim 33 (as can be seen from the Preliminary Amendment), which is within Claim 1, 3, 6, 7, 8, 12, 14, 15, 16, 17, 18, 19, 21, 22, 23, 24, and 26.

Comparison of Example 13 with PAMAM art is provided by present Examples I-V to shown the distinct advantages of these present PEHAN dendrimers.

General Remarks

As it is important to understand these classes of polymers and their differences from other polymers, we provide the following general remarks.

There are different recognized families of dendritic polymers: (A) random hyperbranched; (B) dendrigraft; and (C) dendrimers. Note that dendrimers are one class of dendritic polymers. Sometimes these terms have been used improperly.

Group (A) dendritic polymers are derived from one-pot condensation reactions of AB_n monomers. These dendritic structures are usually moderate to high molecular weight structures and growth is random condensation reactions. These polymers have a polydispersity index $M_w/M_n \approx 2$. This is higher than the present dendrimers.

Group (B) dendritic polymers are achieved by (i) grafting onto [common for tailored structures and topology where grafting sites are introduced on a polymeric substrate followed by coupling with reactive living polymer chains], (ii) grafting from [polymeric substrate is first functionalized to bear a number of reactive groups followed by addition of a monomer to grow the side chains] or (iii) grafting through methods [produces comb-branched polymers].

Group (C) dendritic polymers can be prepared by divergent or convergent methods. The most known dendrimer form is PAMAM dendrimers. Others have now been made.

The book, <u>Dendrimers and Other Dendritic Polymers</u>, eds. J.M.J. Fréchet, D. A. Tomalia, pub. John Wiley and Sons (2001), describes many of these features for dendritic polymers. On page 15 of this book, Fig 1.8 shows these three groups of dendritic polymers as discussed above such that the pictorial illustration aids to understand their differences. Also on page 18, Fig 1.10 shows (B) and (C) differences. On page 19, Fig 1.11 compares the degree of polymerization between (B) and (C) dendritic polymers. On page 34, Fig 1.19 shows the differences in intrinsic viscosities of (A), (B) and (C) dendritic polymers. The difference in density of a dendrimer is attained by whether the branches are symmetrical or not. On page 35, Fig 1.20 shows the significant density difference in 2 such dendrimers. Thus even among (C) dendrimers, there are significant characteristic differences. All these

differences result in physical and chemical differences in the resultant dendritic polymer. Thus they are all distinguishable from each other and are not used interchangeably because of these differences. (Copies of these pages are enclosed.)

WO 96/15778 (Kabanov)

Applicants do not believe that the cited reference WO 96/15778 (Kabanov) is relevant to the present invention for the following reasons:
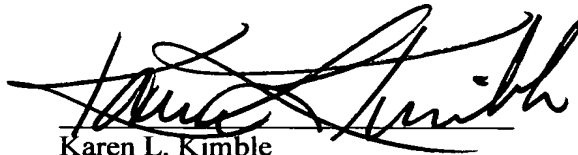
1. Structure XVII (Kabanov) is a block copolymer where i and j are random and not necessarily the same between each arm of the polymer;

2. Structure XVII at positions R^1 and R^2 are either H or CH_3 which are NOT the present [IF] moieties of OH, SH or NH;

3. Structure XVII at positions R^1 and R^2 are either H or CH_3 may not necessarily be the same between each branch as the cited material is formed through a completely different process by basically coupling 4 PEG moieties to a diamine core molecule where each of those PEGs might not be the same;

4. His R^1 is not formed during the process of molecular construction and is not on the same position on each branch as required by our compounds;

5. There is NO [FF] possible in the cited structures;

6. When our structures have no [IF] they MUST have an [EX] which is a very different structure to Structure XVII with amine groups in the chain;

7. Cited Examples XVII, XIX, XX, and XXI are linear block copolymers with amine [IF] but do NOT fit our compounds as there are no [BR] groups, as the present compounds MUST have [IF] and/or [EX] groups and all have [BR];

8. Cited compound XXII is a typo as a tetravalent amine is not possible and NOT an [IF]; and

9.   The polynucleotide part of the cited reference could not form these present compounds.

CONCLUSIONS

Applicants believe that they have responded to all items in this Action. However, if the Examiner has any questions concerning this Response, please contact the undersigned. If there are still unresolved issues, Applicants respectfully request that the Examiner contact the undersigned to expedite progress of the examination and allowance of the claims.

Respectfully submitted,

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Enclosure:
J.M.J. Fréchet, D. A. Tomalia, pub. John Wiley and Sons (2001), at title page and page 15, Fig 1.8; page 18, Fig 1.10; page 19, Fig 1.11; page 34, Fig 1.19; page 35, Fig 1.20

Dendrimers and Other Dendritic Polymers

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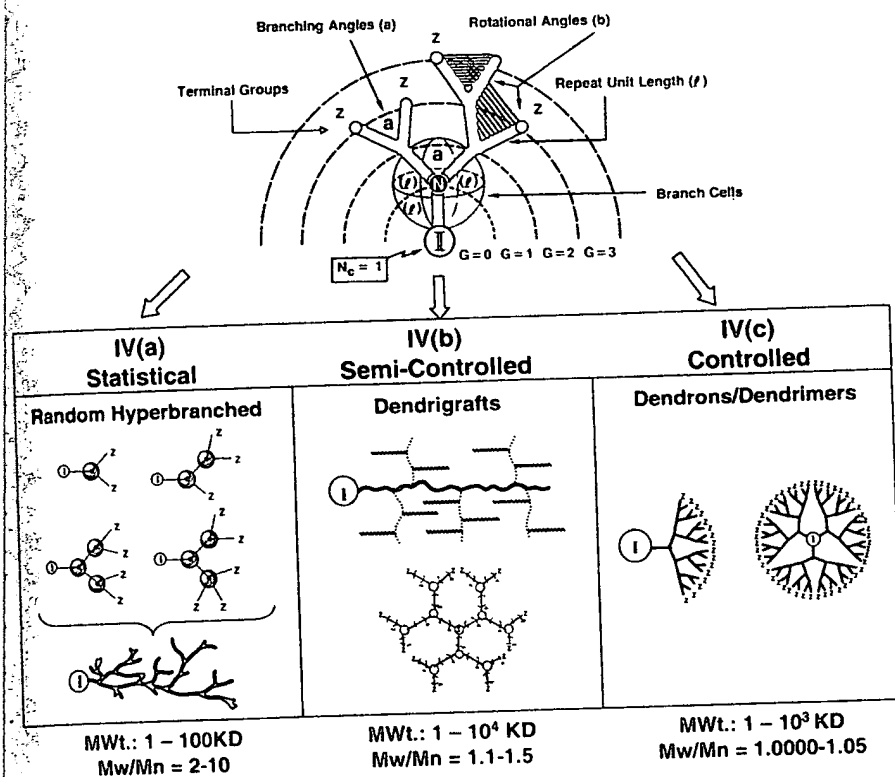
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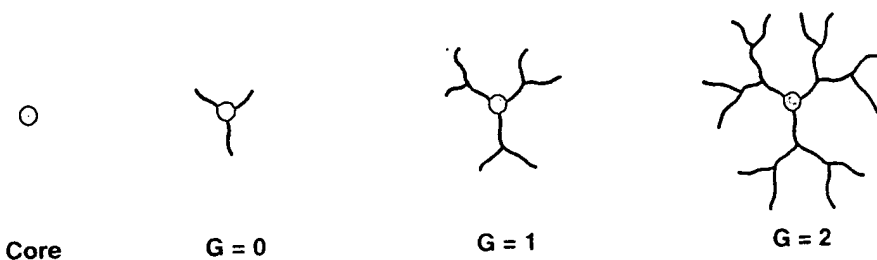
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Figure 1.8 Branch cell structural parameters (a) branching angles, (b) rotation angles, (l) repeat units lengths, (Z) terminal groups and dendritic subclasses derived from branches (IVa) random hyperbranched, (IVb) dendrigrafts and (IVc) dendrons/dendrimers

2.4 RANDOM HYPERBRANCHED POLYMERS

Flory was the first to hypothesize concepts [28, 52], which are now recognized to apply to statistical, or 'random hyperbranched' polymers. However, the first purposeful experimental confirmation of dendritic topologies did not produce random hyperbranched polymers but rather the more precise, structure controlled, dendrimer architecture. This work was initiated nearly a decade before the first examples of 'random hyperbranched' polymers were confirmed independently in publications by Odian/Tomalia [53] and Webster/Kim [54, 55] in 1988. At that time, Webster/Kim coined the popular term 'hyperbranched polymers' that has been widely used to describe this type of dendritic macromolecules.

Hyperbranched polymers are typically prepared by polymerization of AB_x

Dendrimer Architecture

| Core | G = 0 | G = 1 | G = 2 |

Dendrigraft Architecture

| Core | G = 0 | G = 1 | G = 2 |
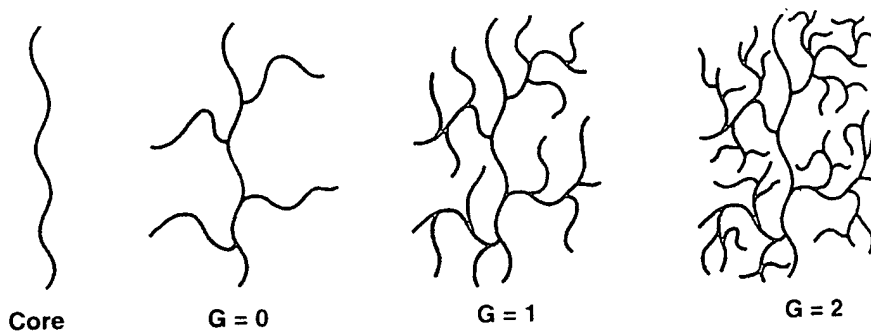
Figure 1.10 Comparison of dendrimer and dendrigraft architecture Generation: 0–2

densities are somewhat arbitrary and difficult to control.

More recently, both Gnanou [70, 71] and Hendricks [72, 73] have developed approaches to dendrigrafts that mimic dendrimer topologies by confining the graft sites to the branch termini for each generation. These methods involve so-called 'graft from' techniques and allow better control of branching topologies and densities as a function of generation. Topologies produced by these methods are reminiscent of the dendrimer architecture (Figure 1.10). Since the branch cell arms are derived from oligomeric segments, they are referred to as 'polymeric dendrimers' [21]. These more flexible and extended structures exhibit unique and different properties compared to the more compact traditional dendrimers. Fréchet and coworkers [74] have used the techniques of living polymerization and a staged polymerization process in which latent polymerization sites are incorporated within growing chains, then used to produce dendrigrafts of mixed composition and narrow polydispersity.

Another exciting development has been the emerging role that dendritic architecture is playing in the production of commodity polymers. A recent report
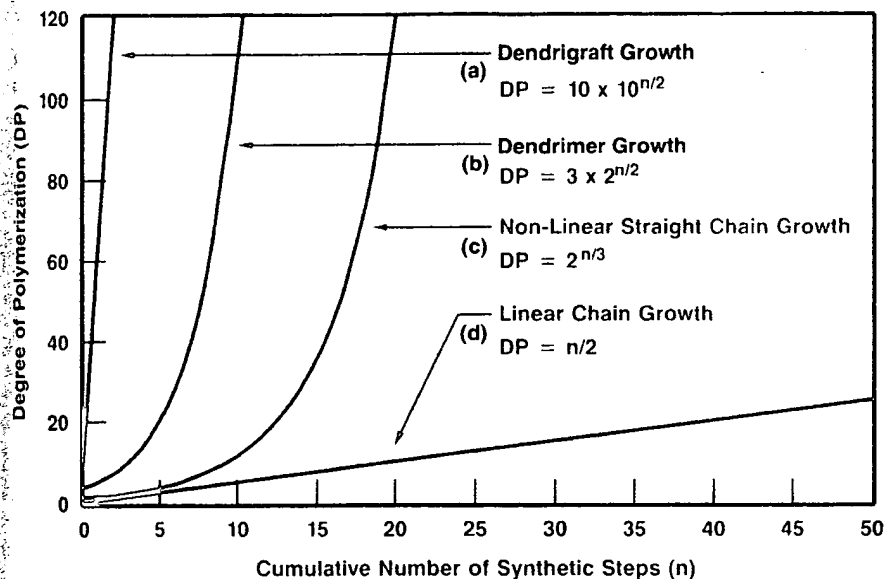
Figure 1.11 Comparison of degree of polymerization as a function of topology and growth process (a) dendrigraft, (b) dendrimer, (c) non-linear straight chain and (d) linear

by Guan *et al.* [24] has shown that ethylene monomer polymerizes to *dendrigraft*-poly(ethylene) at low pressures in contrast to high pressure conditions, which produce only branched topologies. This occurs when using late transition metal or Brookhart catalysts (Figure 1.12). Furthermore, these authors also state that small amounts of *dendrigraft poly(ethylene)* architecture may be expected from analogous early transition metal-metallocene catalysts.

2.6 DENDRONS AND DENDRIMERS

Dendrons and dendrimers are the most intensely investigated subset of dendritic polymers. In the past decade over 2000 literature references have appeared on this unique class of structure controlled polymers. The term 'dendrimer' was coined by Tomalia, *et al.* over 15 years ago in the first reports on poly(amidoamine) (PAMAM) dendrimers [75, 76]. It is derived from the Greek words *dendri*-(branch tree-like) and *meros* – part of). Poly(amidoamine) dendrimers constitute the first dendrimer family to be commercialized and undoubtedly represent the most extensively characterized and best understood series at this time. In view of the extensive literature information in this area, much of the remaining overview will focus on PAMAM dendrimers and will
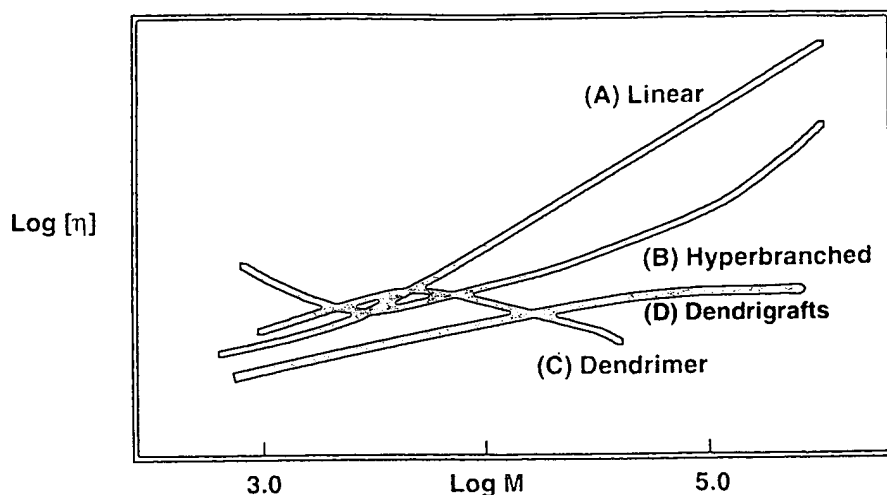
Figure 1.19 Comparison of intrinsic viscosities (log (η)) versus molecular weight (log *M*) for (A) linear, (B) random hyperbranched, (C) dendrimers and (D) dendrigraft topologies. Data for A, B, C adapted from Fréchet *et al.*, Ref. 49.

3. Exponential amplification of terminal functional groups.
4. Persistent nanoscale dimensions/shape as a function of molecular weight (generation).

These features are captured to some degree with dendrigraft polymers, but are either absent or present to a vanishing small extent for random hyperbranched polymers.

3.2 OVERVIEW OF UNIQUE DENDRIMER PROPERTIES – MONODISPERSITY

The monodispersed nature of dendrimers has been verified extensively by mass spectroscopy, size exclusion chromatography, gel electrophoresis and electron microscopy (TEM). As is always the case, the level of monodispersity is determined by the skill of the synthetic chemist, as well as the isolation/purification methods utilized.

In general, convergent methods produce the most nearly isomolecular dendrimers. This is because the convergent growth process allows purification at each step of the synthesis and therefore no cumulative effects of failed couplings are found [85, 89]. Appropriately purified convergent dendrimers are probably the most precise synthetic macromolecules that exist today.

As discussed earlier, mass spectroscopy has shown that PAMAM dendrimers (Figure 1.17) produced by the 'divergent method' are very monodisperse and
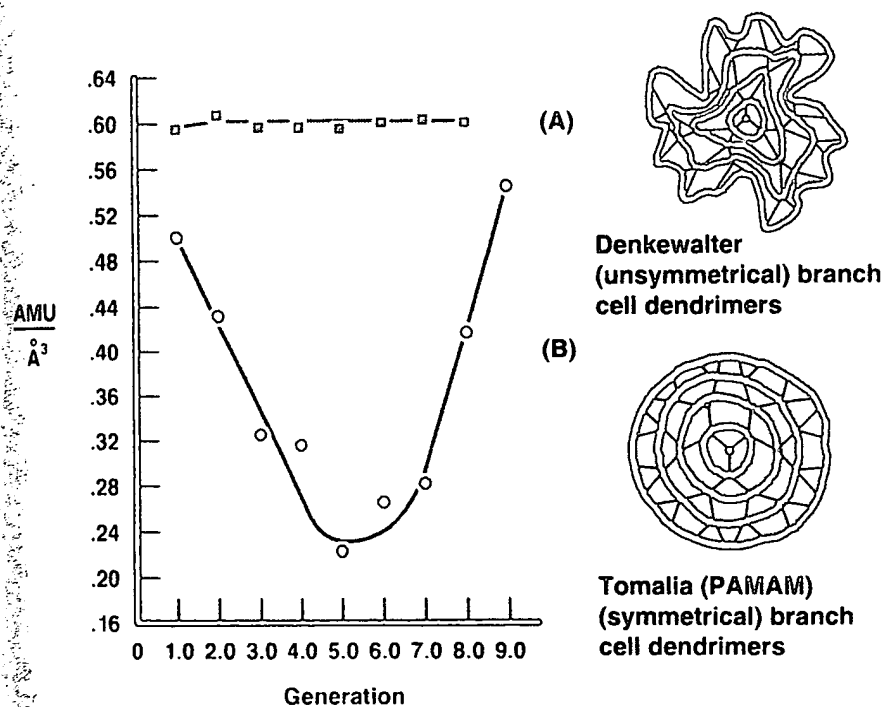
Figure 1.20 Comparison of densities as a function of generation for (A) asymmetrical branch cell in Denkewalter-type dendrimers, (B) symmetrical branch cell in Tomalia-type dendrimers ([densities calculated from experimental hydrodynamic diameters and theoretical, D.A. Tomalia, M. Hall, D.M. Hedstrand, *J. Am. Chem. Soc.*, **109**, 1601 (1987))

have masses consistent with predicted values for the earlier generations (i.e. G = 0–5). Even at higher generations, as one enters the de Gennes dense packed region, the molecular weight distributions remain very narrow (i.e. 1.05) and consistent in spite of the fact that experimental masses deviate substantially from predicted theoretical values. Presumably, de Gennes dense packing produces a very regular and dependable effect that is manifested in the narrow molecular weight distribution.

3.3 UNIMOLECULAR CONTAINER/SCAFFOLDING PROPERTIES

Unimolecular container/scaffolding behavior appears to be a periodic property that is specific to each dendrimer family or series. These properties will be determined by the size, shape, and multiplicity of the construction components that are used for the core, interior and surface of the dendrimer. Higher multiplicity components and those that contribute to 'tethered congestion' will hasten the